REVIEW

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How gait influences frailty models and health-related outcomes in clinical-based and population-based studies: a systematic review

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Abstract

Aging is often associated with a decline in physical function that eventually leads to loss of autonomy in activities of daily living (ADL). Walking is a very common ADL, important for main determinants of quality of life in older age, and it requires the integration of many physiological systems. Gait speed has been described as the 'sixth vital sign' because it is a core indicator of health and function in aging and disease. We reviewed original studies up to June 2020 that assessed frailty in both longitudinal and cross-sectional observational studies, paying particular attention to how gait is measured in older population and how the gait parameter adopted may influence the estimated frailty models and the health-related outcomes of the various studies (i.e. clinical, cognitive, physical, and nutritional outcomes). Eighty-five studies met the search strategy and were included in the present systematic review. According to the frailty tools, more than 60% of the studies used the physical phenotype model proposed by Fried and colleagues, while one-third referred to multi-domain indexes or models and only 5% referred to other single-domain frailty models (social or cognitive). The great heterogeneity observed in gait measurements and protocols limited the possibility to directly compare the results of the studies and it could represent an important issue causing variability in the different outcome measures in both clinical-and population-based settings. Gait appeared to be an indicator of health and function also in frail older adults, and different gait parameters appeared to predict adverse health-related outcomes in clinical, cognitive, and physical domains and, to a lesser extent, in nutritional domain. Gait has the potential to elucidate the common basic mechanisms of cognitive and motor decline. Advances in technology may extend the validity of gait in different clinical settings also in frail older adults, and technology-based assessment should be encouraged. Combining various gait parameters may enhance frailty prediction and classification of different frailty phenotypes.

Keywords Aging; Gait analysis; Health status; Cognition; Physical performance; Diet

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Introduction

Aging can be associated with a decline in physical function that eventually leads to loss of autonomy in daily life activities.[1] In many older persons, such a decline has no explicit connection to a defined medical condition and, often, it does not receive proper medical attention until a late stage. With this evidence, the concept of frailty has gained importance over the past decade because of the population aging and the pressing need to prevent late-life disability and its burdening consequences.[2] In fact, as a general concept, frailty is a clinical condition characterized by reduced capacities in multiple physiological systems, determining a state of increased vulnerability to stressors and susceptibility to adverse health-related outcomes (e.g. functional decline, falls, hospitalization, and death).[3] The causes of frailty are not fully understood. A pathophysiological pathway that shows similarities with, but is not identical to, the aging process has been recently reported in frail older adults with cancer.[4] However, even though the underlying mechanisms of frailty are not fully understood, frailty is acknowledged to be not only a biological or physiological state but also a multidimensional concept.[5] Indeed, this clinical condition may include sensorial, physical, social, cognitive, psychological/depressive, and nutritional phenotypes.[6] Within each of the physical, psychological, and social dimensions, various risk factors or determinants for frailty exist. These factors include (i) a physical dimension: nutritional status,[6] physical activity,[7,8] mobility,[9] strength,[10] and energy; (ii) a neuropsychological dimension: cognition[11,12] and mood[13]; and (iii) a social dimension: lack of social contacts and social support.[14,15]

In particular, mobility is the most studied and most relevant physical ability affecting quality of life with strong prognostic value for disability and survival.[16] In fact, walking is a component of activity of daily living (ADL), and it is important for the main determinants of quality of life in older age such as maintaining independence in ADL, enjoying an adequate level of social interaction, and retaining good emotional vitality.[17] Although it appears to be an entirely unsophisticated automated motor task, maintaining normal gait is a much complex process requiring intact multisystem function and coordination.[18,19] Actually, effective gait requires the integration of many physiological systems, including the central and peripheral nervous systems that create and execute the motor program, the musculoskeletal system that moves and supports the body, and the cardio-pulmonary function that provides perfusion of adequate nutrients and oxygen to all of the integrated parts. With an increase in age, physiologically characterized by a decrease in lean mass, bone mineral density and, to a lesser extent, fat mass disturbances in either one of these functions[20,21] affect parameters of gait (i.e. speed, stride length, and swing time), thus resulting in abnormal gait.[22]

Gait speed has been described as the 'sixth vital sign' because it is a core indicator of health and function in aging and disease,[23–27] as confirmed in 2009 by the International Academy on Nutrition and Aging Task Force[28] and in 2019 by the Canadian Consortium on Neurodegeneration in Aging.[29] However, because most of the studies have relied on qualitative measurements in a standardized setting, a great heterogeneity in the adopted protocols emerged and it made difficult to compare the results. Furthermore, it has not been yet clarified whether parameters of gait performance other than gait speed may also play a role. In fact, although gait speed showed high effect size for discriminating between frailty status groups,[30] slow gait is a nonspecific variable, which is also linked to aging and other aging-related gait disorders. In addition, emerging evidence has shown how many genetic and non-genetic factors (environment and disease) are likely to affect quantitative complex traits such as gait speed.

The complexity and the multidimensionality of gait make it difficult to clarify its real role in a potentially frail population. Thus, the objectives of the present systematic review were

- to highlight the great heterogeneity in the protocol and the parameters adopted when dealing with gait aspects, paying attention to its role as a predictor for frailty or an outcome's measurement;
- to summarize all the information related to how gait and/or related parameters have been measured in the different frailty models or tools;
- to report how the gait and/or related parameters adopted may have influenced the estimated frailty in both population-and clinical-based settings; and
- to show how the gait and/or related parameters affected the health-related outcomes of the various studies, that is, clinical (mortality, hospitalization rate, geriatric syndromes, functional status, and quality of life), cognitive [mild cognitive impairment (MCI), Alzheimer's disease (AD), dementia, and neuropsychological tests], physical (laboratory-based biomarkers, physical activity, sensorial impairments, and falls), and nutritional outcomes (malnourished status assessed through diet energy/nutrient intakes and/or validated scales).

Methods

Information sources, search strategy, and eligibility criteria

The present review was conducted following PRISMA guidelines.[31] No protocol for the study has been published. Two of the authors (I. B. and L. L.) independently conducted an extensive literature search. The databases PubMed, Scopus, and ISI Web of Knowledge were screened using the following combination of keywords: ('gait' OR 'gait analysis') AND ('frailty') AND ('cognitive' OR 'cognition' AND 'impairment'). Observational studies considered as eligible for the present review were those that met the following inclusion criteria: published as an original article in scientific journals up to June 2020; available entirely in English; defining a frail population/cohort through a validated frailty model[32]; indicating the assessment of gait impairment; indicating a cognitive screening; and involving population aged >50 years.

In relation to the classification of frail individuals, we decided to consider primary frailty as defined by Xue and colleagues[33]: a unique clinical entity in itself and its underlying pathophysiology is separable from other disease-specific processes. We then excluded all the studies involving secondary frailty, where frailty is clinically in conjunction with signs and symptoms of a pre-existing disease (e.g. congestive heart failure) or a direct consequence of the pre-existing disease or an acute health event (e.g. hip fracture).[33] The exclusion criteria adopted were as follows: repeated in the databases; included as editorials, reviews, reports of experience, abstracts published in events, monographs, dissertations or theses, review studies, and meta-analyses; involving only older people with a specific disease (hypertension, diabetes, arthritis/arthrosis, cardiovascular diseases, AD, and Parkinson's disease); and involving treatment or intervention. Neither randomized controlled trials nor interventional studies have been considered as eligible. Potentially relevant articles were identified by reading the abstract and, if necessary, by reading the full text version of the article.

Risk of bias was assessed using the checklist published by the US National Heart, Lung and Blood Institute for observational cohort and cross-sectional studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools), considering all the criteria except those related to the outcome (Items 8 and 11). In order to deal with publication bias, we did not limit our search to only journal articles indexed in cited repositories, but we searched for results through other routes including references on potential relevance to be added to the review if inclusion criteria were met.

Data extraction

Firstly, the following information was collected from the selected studies: location (country) where the study was conducted and number and characteristics of the sample involved. Secondly, frailty tools, gait protocols, objectives, outcomes, and main findings were extracted. The procedures for selection of eligible studies involved reading the titles, abstracts, and the studies in full. Studies that did not meet the inclusion criteria or did not address the research question were excluded.

Frailty models and domains

In the present study, we chose to focus on the physical, psychological, and social domains of frailty to reflect the multidimensional nature of this concept. Based on earlier systematic review articles,[4] the factors nutritional status, physical activity, mobility, strength, energy (physical domain), cognition, mood (psychological domain), and social relations/social support (social domain) were selected as essential factors in frailty assessment (*Table* 1). It was judged whether the frailty tools used for the diagnosis covered these frailty factors. In addition, for frailty tools, we identified two categories: multi-domain and single-domain frailty tools. The multi-domain tools focus on a broad concept of frailty and include losses in the medical, psychological, cognitive, functional, and social domains. On the other hand, the single-domain tools solely focus on one frailty phenotype such as social frailty, cognitive frailty, or physical frailty.

Table 1 Frailty instrument domains

Frailty domain	Operationalization
Nutritional status	Body weight Appetite Body mass index Nutritional assessment
Physical activity	Level of physical activity Leisure time physical (group) activity
Mobility	Difficulty or needing help walking/moving in and around the house Gait speed
Energy	Tiredness Energy level (e.g. exhaustion/fatigue)
Strength	Lifting an object that weighs over 5 kg Weakness in arms and/or legs Performing chair stands Climbing stairs Grip strength Calf muscle circumference
Mood	Depression/depressed mood Sadness Anxiety Nervousness
Cognition	Memory problems Diagnosed dementia or cognitive impairment
Social relations/social support	Social resources (when help is needed, can someone provide this?) Emptiness/missing people around

Gait protocols

All items regarding gait or walking abilities were extracted from the following protocols. We looked for the kind of test adopted to measure mobility performance, the parameters analysed, and if any technological devices have been used. We reported whether:

- Gait speed was aimed over a short distance (maximum 20 m); reported as a continuous measure with measures of central tendency (mean and/or median) and distribution [standard deviation (SD) and/or range]; reported as categorical measures; measured as a straight walk on a level indoor surface with no turns (excluding walking on treadmill); and timed under same conditions (i.e. while performing tasks accepted only if single tasks were reported too).
- Dual-task gait, defined here as walking while performing a cognitively demanding task, has been performed to isolate the cognitive component of locomotion and provide insights into the mechanisms of motor control.
- Gait variability, fluctuations in temporal and spatial gait parameters, have been measured.

Health-related outcomes

Study outcomes have also been extracted and grouped according to the nature of the measure (as shown in *Figure* 1):

i *clinical domain* in case of measurable changes in health, function, or quality of life that result from the study sample (i.e. hospital readmission rates or by agreed scales and other forms of measurement, disability, mortality, etc.);
ii *cognitive domain* when a diagnosis of MCI, AD, and dementia has been made or cognitive impairment in specific domains;
iii *physical domain* when related to changes in physical variables (i.e. sensorial impairments, balance, falls, laboratory-based biomarkers, and physical abilities); and
iv *nutritional domain* when related to a diagnosis of malnourished status assessed through diet energy/nutrient intakes and/or validated scales.

Results

Included studies

At first, the literature search generated 309 articles among the three databases consulted (Supporting Information, *Table S1*). After combining the results, 229 articles were present in our database. Twenty-three studies were identified through other sources and included in the process. While screening all titles and abstracts, 124 hits were excluded because they were not referenced as original journal articles, and 80 were excluded because they were duplicates. Then another seven papers were further excluded because (i) they focused on a different topic, (ii) they included gait tests not designed for a frail population, and (iii) different populations were investigated. Finally, 85 studies were included in the present systematic review according to the inclusion criteria. A detailed overview of this process can be found in *Figure* 2.

The research questions of the included papers were clearly stated, and the study population was clearly specified and defined. The authors assessed a sufficient participation rate of eligible persons, and all the subjects were recruited from similar populations, with prespecified inclusion and exclusion criteria being applied uniformly to all participants. Most of the studies did not provide neither sample size justification nor power description. However, they included such limitations in the Discussion section. Because the inclusion criteria for the selected papers considered non-clinical population, the outcome assessors were blinded to the exposure status of participants, although the authors did not clearly state it in the text. For longitudinal studies, the loss to follow-up was less than 20%. All the included studies considered key

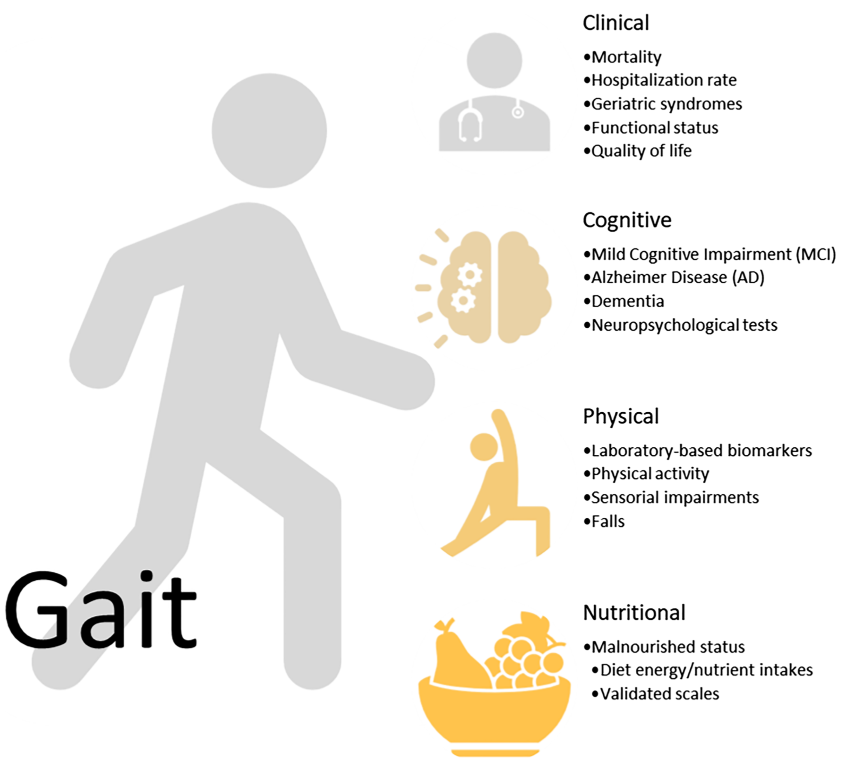

Figure 1 Health-related outcomes extracted and grouped according to the nature of the measure (clinical, cognitive, physical, and nutritional) in relation to gait.

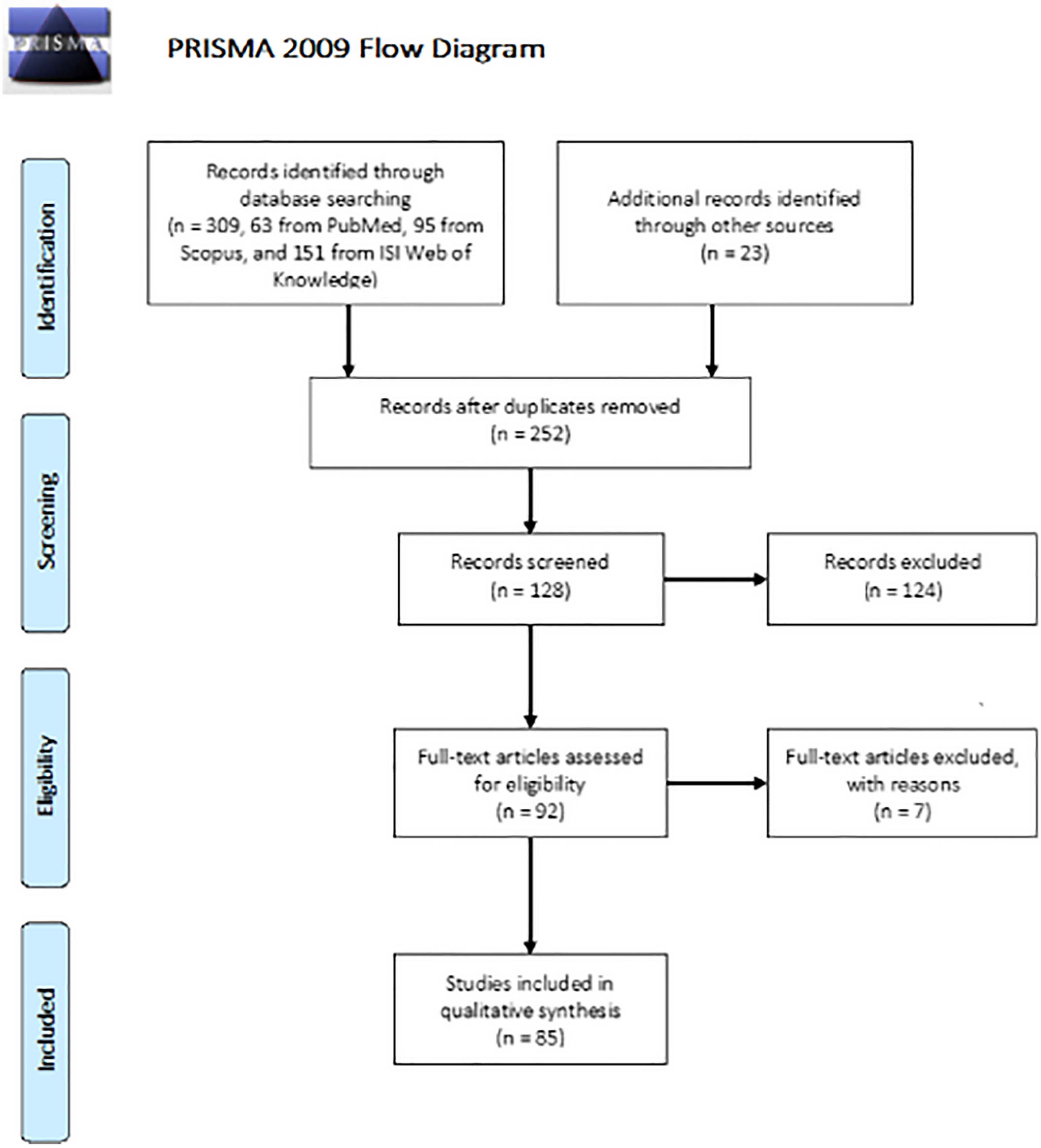

Figure 2 PRISMA 2009 flow diagram of retrieved and selected studies.

potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s) (*Table S2*).

The characteristics of the selected studies indicated there were more articles published in the last 5 years (n = 61, 71.8%). Regarding sample size, there were variations in quantity, ranging from 43 older subjects in a cross-sectional study to 49 283 participants in a multicentre cohort study. There was a predominance of cross-sectional studies (n = 53, 62.4%), with a slight prevalence of population-based studies. According to the frailty phenotype, 57 studies used the physical phenotype model proposed by Fried and colleagues,[34] a single-domain frailty tool. Twelve of them assessed also other frailty phenotype models in both physical and cognitive domains as did other 17 studies. Only four articles referred to other single-domain frailty tools (social or cognitive). It is worth noting that several articles considered physical function deficits to be characterized by slow walking speed or/ and lower grip strength. According to the gait protocol, half of the study used gait speed as parameter for slowness (expressed in metre per second) and as indicator of gait performance for additional assessment. One-third of the study used gait time, measured in seconds. We did not observe a preferred protocol for measuring gait speed; however, the majority of the studies used 2.4, 4.6, and 6 m walks. The cut-off values for each measurement also differed from one study to the other. Twenty per cent of the studies did not refer to any specific cut-off value, while 12.9% considered 1 m/s as the discriminative gait speed to separate frailty subjects from healthy pairs (*Table S3*).

A detailed overview of the included studies is reported in *Table* 2 where we showed the general information of the study (location, type, sample number, and age range), the frailty model adopted (index/phenotype and domain) with the related gait parameters and protocols, and finally, the relative estimated relationships to the study outcomes. In *Figure* 3, we showed the distribution of the included articles in terms of frailty models (and related domains) in relation to the selected gait parameters and protocols. *Figure* 4 depicted the distribution of the included articles in relation to the health-related outcomes investigated and the gait parameters adopted. We then summarized the major findings each included study reported according to both the influence of gait in the frailty models adopted and the role of gait parameters with respect to selected health-related outcomes.

Influence of gait in different frailty models

Among the 18 studies that reported as outcome the identification of frailty status in the older population, only few of them investigated the specific influence of gait in relation to the frailty model/phenotype. Other studies that revealed these associations were those where new frailty phenotypes have been proposed (*Table* 2, last column).

Raji and colleagues[40] showed that the percentage of participants who became frail from non-frailty status by slowness (walk speed) criterion alone increased from 17.6% to 25% in people with low cognition and from 15.8% to 18.1% in normal population. Garcia-Garcia and colleagues[44] reported that slowness was the prevalent criterion of the frailty status (24.1% in 1972 subjects) in the Toledo Study on Healthy Aging, like the results obtained by Chen and colleagues[63] from the Sasaguri Genkimon Study (17.1% in 1527 older people). Other studies reported higher prevalence of slowness among frailty items,[75,83] while Yoon and colleagues[104,105] reported lower percentage, although the sample size was significantly reduced.

Two studies focused also on impaired balance as a potential contributor to frailty, with conflicting results: Kang and colleagues[37] presented the first report on quantitative posturography measures in frail individuals during a dual-task paradigm showing that the index of complexity [odds ratio (OR): 0.303; 95% confidence interval (CI): 0.114–0.805], centre of pressure path length (OR: 1.002; 95% CI: 1.000–1.004), and root mean square (RMS) of high-pass filtered sway signal (OR: 10.3; 95% CI: 1.312–80.76) were significantly associated with frailty, while Davis and colleagues[43] concluded that balance and mobility were not sufficient to define a participant as frail.

Thirteen studies showed the influence of gait parameters in relation to different frailty instruments. In particular, Cherubini and colleagues[64] found that only slow gait speed (OR: 19.65; 95% CI: 4.69–82.35) and mobility issues (OR: 18.04; 95% CI: 3.11–104.78) were significantly associated with the condition of frailty in the absence of disability. Badrawasi and colleagues[79] found that rapid pace gait speed was a significant frailty predictor. Hartley and colleagues[87] reported a strong association between higher admission Clinical Frailty Scale (CFS)[120] and lower discharge usual gait speed (OR: 0.57; 95% CI: 0.50–0.65), not explained by variation in age, sex, presence of cognitive impairment, or illness acuity, thus providing the CFS maybe a valid measure of frailty in clinical settings. Lee and colleagues[90] found that while use of either gait speed or grip strength alone was sensitive and specific as a proxy for the Fried frailty phenotype, the dual-trait measure of gait speed with grip strength was accurate, precise, specific, and more sensitive than individual traits and other possible dual-factor combinations. Montero-Odasso and colleagues[75] found that only slow gait was cross-sectionally associated with being cognitively impaired (OR: 2.14; 95% CI: 1.13–4.05). Shimada and colleagues[101] developed a new operational definition of cognitive frailty as the concomitant presence of physical frailty (as slow walking speed or muscle weakness), cognitive impairment, and a sign of impairment in word list memory, attention, executive function, or processing speed in the National Center for Geriatrics and Gerontology-Functional Assessment Tool. However, no data were shown about the influence of slowness in this new operational frail model. Yu and colleagues[106] reported that subjects with cognitive frailty were characterized by lower gait speed. Zhong and colleagues[107] showed that older adults had significantly decreased speed and step frequency under the dual cognitive task condition. Pre-frail older adults showed significantly decreased speed, mediolateral RMS, vertical RMS, anteroposterior RMS, vertical amplitude variability, and vertical step regularity compared with non-frail older adults ($P < 0.05$). Zhou and colleagues[116] confirmed previous studies demonstrating that gait speed is the most important indicator of the frailty syndrome (OR: 0.082; 95% CI: 0.007–0.947).

Four studies explored the ability of slow gait speed in contributing to the definition of frailty status according to Gerontopole Frailty Screening Tool,[47] comprehensive geriatric assessment,[60] 'Vozrast ne pomekha',[102] and targeted geriatric assessment,[94] concluding that gait speed was the most frequently observed frailty criterion in their population and thus supporting the cycle of frailty hypothesis put forth by Fried and colleagues.[34] Only Tsutsumimoto and colleagues[92] investigated the association between social frailty and physical function, defined through gait speed and grip strength, and they found that gait speed also varied between social frailty groups (all *P*s for trend < 0.001).

Table 2 Included studies in the systematic reviews of frailty instruments in relation to mobility domain in terms of adopted gait parameters and protocols and relative estimated relationships to study outcomes (underlined variables refer to additional measurements not used in frailty tools)

Reference	Study	Site	Age (years)	Sample	Frailty tool	Frailty domain	Mobility	Gait protocol (walk)	Outcome	Gait influence on outcome
Bartali *et al*., 2006[35]	LP	IT	>65	1299	FPFC	SP	GT (s)	4.6 m	Dietary intake	OR: 1.64; 95% CI: 0.95 to 2.84
Rothman *et al*., 2008[36]	LP	USA	>70	754	FPFC	SP	GT (s)	3 m	Long-term NH stay Injurious falls Death ADLs	HR: 3.8; 95% CI: 3.0 to 4.9 HR: 5.9; 95% CI: 3.5 to 9.8 HR: 2.5; 95% CI: 1.6 to 4.0 HR: 2.7; 95% CI: 2.0 to 3.7
Kang *et al*., 2009[37]	CP	USA	>70	550	FPFC	SP	GT (s) COP (single/dual)	4 m	Frailty status	
Shimada *et al*., 2009[38]	CP	JP	>65	3795	FPFC	SP	GS (m/s) CST (s), OLS (s), FRT (cm), TWT (steps), TUG (s)	4.6 m	Falls	RR_{CWS}: 1.82; 95% CI: 1.16 to 2.85 RR_{TWT}: 1.49; 95% CI: 0.95 to 2.33
Boyle *et al*., 2010[39]	LC	USA	>50	761	CFM	SP	GT (s)	2.4 m	CD	HR_{MCI}: 1.27; 95% CI: 1.11 to 1.45
Raji *et al*., 2010[40]	LP	USA[a]	>65	942	FPFC	SP	GT (s)	4.8 m	Frailty status	
Auyeung *et al*., 2011[41]	LP	CN	>65	2737	NMC	SP	StL (m) GS (m/s) nGS (m/s) 5CST (s)	6 m	CD	ADU_{StL}: 0.162 (0.013 to 0.309)
Beasley *et al*., 2011[42]	LP	USA	65–79	24 417	FPFC	SP	Rand-36 Physical Function Scale		FFQ	
Davis *et al*., 2011[43]	LP	CA		1295	FI-CGA	M	TUG(s) FR (m)		Frailty status	
Garcia-Garcia *et al*., 2011[44]	LP	ES	>65	2448	FPFC	SP	GS (m/s) (SPPB) GS (m/s), CST (s), Sway	3 m[b]	Frailty status	
Chang *et al*., 2012[45]	CP	TW	>65	374	FPFC	SP	TUG (s)		HRQoL	
Langlois *et al*., 2012[46]	CC	CA	>60	83	FPFC+ MPPT+ CFS-FI	M	TUG (s) GS (m/s) 6MWT	7.6 m	Physical capacity Cognition QoL	
Subra *et al*., 2012[47]	CP	FRa	>65	160	FPFC GFST	SP M	GT (s) SPPB	4 m	Frailty status	
Talegawkar *et al*., 2012[48]	LP	IT	>65	690	FPFC	SP	GT (s)	4.6 m	MDS	OR_{HIGH}: 0.48; 95% CI: 0.27 to 0.86
Yassuda *et al*., 2012[49]	CP	BR	>65	384	FPFC	SP	GT (s)	4.8 m	Cognitive function	OR_{VF}: 2.58; 95% CI: 1.17 to 5.68 OR_{CDT}: 2.69; 95% CI: 1.10 to 6.55
Bollwein *et al*., 2013[50]	CP	DE	>75	206	FPFC	SP	GT (s)	4.6 m	MDS	OR: 0.29; 95% CI: 0.09 to 1.00
Casas-Herrero *et al*., 2013[51]	CC	ES	>75	43	FPFC	SP	GT (s) GS (m/s) (single/dual) TUG (s) FICSIT-4	4.8 m 5 m	Frailty status Functional tests Muscle strength Falls	
McGough *et al*., 2013[52]	CP	USA	>70	201	FPFC	SP	GT (s)	2.4 m	Cognitive function	

(*Continues*)

Table 2 (continued)

Reference	Study	Site	Age (years)	Sample	Frailty tool	Frailty domain	Mobility	Gait protocol (walk)	Outcome	Gait influence on outcome
Shimada *et al.*, 2013[53]	CP	JP	>70	5104	FPFC	SP	GS (m/s)	2.4 m	Cognitive function	
Alexandre *et al.*, 2014[54]	LP	BR	>60	1413	FPFC	SP	SPPB (m/s)	2.4 m	SE (age) BE (sedentary) HS (stroke, MMSE) A-PH (HGS)	$\mathrm{OR}_{♂}$: 1.09; 95% CI: 1.06 to 1.12 $\mathrm{OR}_{♀}$: 1.12; 95% CI: 1.09 to 1.15 $\mathrm{OR}_{♀}$: 4.18; 95% CI: 2.67 to 6.53 $\mathrm{OR}_{♂}$: 2.87; 95% CI: 1.64 to 5.03 $\mathrm{OR}_{♂}$: 0.95; 95% CI: 0.91 to 0.99
Brown *et al.*, 2014[55]	LP	DK, SW	>75	1027	FPFC	SP	GS (m/s)	10 m	Depression Mortality	$\mathrm{HR}_{♀}$: 1.99; 95% CI: 1.4 to 2.8 $\mathrm{HR}_{♂}$: 1.85; 95% CI: 1.3 to 2.6 $\mathrm{HR}_{♀}$: 1.84; 95% CI: 1.1 to 3.2
León-Muñoz *et al.*, 2014[56]	LP	SP	≥60	1815	FPFC	SP	GT (s)	3 m	MEDAS MDS	OR: 0.53; 95% CI: 0.35 to 0.79
O'Halloran *et al.*, 2014[57]	CP	IE	>50	4317	FPFC	SP	GS (m/s)	4.8 m[b]	SART	OR: 1.39; 95% CI: 1.10 to 1.76 OR_{65+}: 1.31; 95% CI: 1.08 to 1.59
Yamada *et al.*, 2014[58]	CC	EU	>75	4007		M	Balance		SI	$\mathrm{OR}_{\mathrm{Single}}$: 1.27; 95% CI: 1.07 to 1.52 $\mathrm{OR}_{\mathrm{Dual}}$: 1.35; 95% CI: 1.11 to 1.64
Cadore *et al.*, 2015[59]	CC	ES	>75	64	FPFC	SP	GS (m/s) (single/dual) TUG (s) (single/dual)	5 m	Frailty status CI	
Cakmur *et al.*, 2015[60]	CP	TR	>65	168	FPFC CGA	SP	GT (m/s)	6 m	Frailty status Physical health	
Camicioli *et al.*, 2015[61]	CC	CH	>65	216	FPFC	SP	GT (s)	20 m	Handwriting task	
Chan *et al.*, 2015[62]	LP	CH	≥65	2724	FRAIL	M	Inability to walk one block		DQI-I MDS	
Chen *et al.*, 2015[63]	CP	JP	>65	1527	FPFC	SP	GT (s)	5 m	Frailty status	
Cherubini *et al.*, 2015[64]	CC	EU	>65	109	FPFC GFST	SP M	GT (s)	4 m	Frailty status	OR: 22.50; 95% CI: 6.27 to 80.74 OR: 19.65; 95% CI: 4.69 to 82.35
Doi *et al.*, 2015[65]	LP	JP	>65	3355	CS + PF	M	GS (m/s)	2.4 m	IGF-1	HR: 1.27; 95% CI: 0.87 to 1.85 $\mathrm{HR}_{\mathrm{MCI,SG}}$: 1.81; 95% CI: 1.07 to 3.05
Doi *et al.*, 2015[66]	LP	JP	>65	3482	CS + PF	M	GS (m/s)	2.4 m	Incident disability (LTCI)	HR: 2.32; 95% CI: 1.41 to 3.81 $\mathrm{HR}_{\mathrm{mMCI,SG}}$: 3.48; 95% CI: 1.8 to 6.8 $\mathrm{HR}_{\mathrm{sMCI,SG}}$: 2.46; 95% CI: 1.2 to 5.0
Doi *et al.*, 2015[67]	CP	JP	>65	3400	CS + PF	M	GS (m/s)	2.4 m	Falls	$\mathrm{OR}_{\mathrm{MCI}}$: 1.99; 95% CI: 1.08 to 3.65 OR: 1.79; 95% CI: 1.05 to 3.06

(*Continues*)

Table 2 (continued)

Reference	Study	Site	Age (years)	Sample	Frailty tool	Frailty domain	Mobility	Gait protocol (walk)	Outcome	Gait influence on outcome
Jotheeswaran *et al.*, 2015[68]	LP	[c]	>65	13 924	FPFC MFI	SP M	GT (s)	5 m	Incident dependence Mortality	IRR: 1.28; 95% CI: 1.12 to 1.47 IRR: 1.30; 95% CI: 1.05 to 1.61 HR: 1.36; 95% CI: 1.21 to 1.51
Makizako *et al.*, 2015[69]	LP	JP	>65	4341	FPFC	SP	GT (s)	2.4 m	Incident disability	HR: 2.32; 95% CI: 1.62 to 3.33
Shimada *et al.*, 2015[70]	LP	JP	>65	4081	FPFC	SP	GS (m/s)	2.4 m	Incident disability (LTCI) MMSE	$HR_{Pre\text{-}frail}$: 3.62; 95% CI: 2.19 to 5.96 HR_{Frail}: 4.68; 95% CI: 2.72 to 8.05 $HR_{Pre\text{-}frail}$: 3.2; 95% CI: 1.8 to 5.6 HR_{Frail}: 3.8; 95% CI: 2.0 to 7.2
Tabue-tuego *et al.*, 2015[71]	LP	FRa	>65	1365	CS + PF	M	GS (m/s)	6 m	Mortality IST Fall CES-D	HR: 1.07; 95% CI: 1.01 to 1.13 OR: −0.03; 95% CI: −0.05 to −0.01 OR: 0.52; 95% CI: 0.23 to 0.81 OR: 0.60; 95% CI: 0.13 to 1.01
Doi *et al.*, 2016[72]	LP	JP	>65	4133	SS	SS	GT (s)	2.4 m	IGF-1	HR: 1.72; 95% CI: 1.06 to 2.81
Malini *et al.*, 2016[73]	CP	BR	>65	742	PF	SP	GS (m/s)	4.6 m	Falls	OR: 1.64; 95% CI: 1.04 to 2.58
Martínez-Ramírez *et al.*, 2016[74]	CC	ES	>75	41	FPFC	SP	GS (m/s) GT (s), GReg, GSym, RMS, ApEn, HaR, THD	5 m[b]	Gait performance	
Montero-Odasso *et al.*, 2016[75]	LP	CA	>65	252	FPFC CF	M	GS (m/s)	4 m[b]	Incident dementia	HR: 35.9; 95% CI: 4.0 to 319.2 HR: 14.8; 95% CI: 1.2 to 175.8
Veronese *et al.*, 2016[76]	LP	IT	>65	3099	CS	SC	GS (m/s) CST (s) SPPB 6MWT (m)	4 m	Cognitive function	OR_{CI}: 1.52; 95% CI: 1.07 to 2.37 OR_{CD}: 1.97; 95% CI: 1.13 to 3.43
Arjuna *et al.*, 2017[77]	CP	ID	>65	527	FRAIL	M	'Did you have any difficulty going up 10 steps alone?' GS (m/s)	3 m	Nutritional status CS	
Ayers *et al.*, 2017[78]	LP	USA	>65	937	FPFC	SP	GS (m/s)	8.5 m[b]	Apathy	HR: 2.11; 95% CI: 1.37 to 3.25
Badrasawi *et al.*, 2017[79]	LP	MY	>60	574	FPFC	SP	GT (s) TUG (s), 5CST (s), AltSTEP (s), GS (m/s) (normal/fast)	4.6 m[b]	Frailty status	OR: 2.72; 95% CI: 1.45 to 5.12 OR: 3.24; 95% CI: 1.38 to 7.60
De Cock *et al.*, 2017[80]	CC	BEl	>50	535	FI-CGA	M	TUG (s), CST (s), FR (s) GS (cm/s) CAD, StW, StWvar, Sw DTC	6.1 m[b]	Cognitive function	
Dokuzlar *et al.*, 2017[81]	CC	TR	>60	335	FPFC FRAIL	SP		4 m	Vitamin B12 deficiency	
Fougère *et al.*, 2017[82]	CP	FRa	>70	1620	FPFC	SP	GS (m/s)	4 m	MCR	OR: 1.89; 95% CI: 1.55 to 2.32
Fougère *et al.*, 2017[83]	CC	FRa	>70	200	GFST FPFC	M SP		4 m	Screening	
	CC	PT	>65	119	FPFC	SP	GT (s)	4.6 m	PFF	

(*Continues*)

Table 2 (continued)

Reference	Study	Site	Age (years)	Sample	Frailty tool	Frailty domain	Mobility	Gait protocol (walk)	Outcome	Gait influence on outcome
Furtado *et al.*, 2017[84]							30 s CST (#), 30-AC, agility–dynamic balance, 2 m STEP	2.44 m	Frailty status	
Garcia-Cifuentes *et al.*, 2017[85]	CP	MX	>65	1564	MD	SP	GS (m/s)	3.4 m	CI	OR: 2.76; 95% CI: 1.83 to 4.15
Hanton *et al.*, 2017[86]	CC	USA	>65	43	FPFC	SP	GS (m/s)	4 m[b]	Step count GS Activity count	
Hartley *et al.*, 2017[87]	CC	UK	>75	741	CFS-FI	M	GS (m/s)	6 m	Frailty status Cognitive function	OR_{CFS-FI}: 0.57; 95% CI: 0.50 to 0.65 OR_{AMT4}: 1.20; 95% CI: 1.07 to 1.34
Hernandez-Luis *et al.*, 2017[88]	CC	ES	>60	298	FPFC CFS-FI	SP M	GS (m/s) 5CST (s) BAL	10 m	Short-term survival Medium-term survival Long-term survival	$HR_{HGS/GS}$: 2.55; 95% CI: 1.2 to 5.4 HR: 3.43; 95% CI: 1.50 to 7.83 $HR_{HGS/GS}$: 1.81; 95% CI: 1.2 to 2.8 $HR_{HGS/GS}$: 5.37; 95% CI: 1.3 to 22.4
Hooghiemstra *et al.*, 2017[89]	LC	NL	>55	309	PF	SP	GS (m/s)	4.6 m	Cognitive function	$HR_{MCI,>65}$: 1.49; 95% CI: 1.0 to 2.2 HR_{MCI}: 1.62; 95% CI: 0.93 to 2.81
Lee *et al.*, 2017[90]	CC	USA	>75	516	FPFC	SP	GT (s)	4 m	Frailty status	PPV: 87.5; 95% CI: 66.5 to 96.7
Nyunt *et al.*, 2017[91]	CP	JP	>55	1938	FPFC	SP	GS (m/s)	6 m	CI	OR: 1.68; 95% CI: 1.02 to 2.79 OR_{POMA}: 3.71; 95% CI: 1.62 to 8.46
Tsutsumimoto *et al.*, 2017[92]	CP	JP	>55	4425	SF	SS	GS (m/s)	2.4 m	CS PF	
Wei *et al.*, 2017[93]	CP	CH	≥55	6045	FPFC	SP	POMA	6 m	MNA-SF NSI	
Aliberti *et al.*, 2018[94]	CC	BR	>60	534	TaGA ISAR FPFC FI-CGA (40 items)	M	GS (m/s)	4.5 m	TaGA score	LWK: 0.62; 95% CI: 0.46 to 0.79
De Cock *et al.*, 2018[95]	CC	BEI	>70	516	FI-CGA	M	TUG (s), FRT (s) GS (m/s), StepVar, SwVar, nStep	[b]	CS	
Doi *et al.*, 2018[96]	LP	JP	>65	3937	CS + FPFC	M	GS (m/s)	2.4 m	Incident dementia	HR_{MCI-SG}: 3.88; 95% CI: 2.5 to 6.1
Doi *et al.*, 2018[97]	CP	JP	>65	4133	FPFC	SP	GS (m/s)	4.6 m	IGF-1	
Hsueh *et al.*, 2018[98]	CC	TW	>65	205	FPFC	SP	GS (m/s)	4.6 m	Dementia	OR: 12.3; 95% CI: 1.7 to 87.7
Lee *et al.*, 2018[99]	CP	KR	>66	49 283	FPFC	SP	TUG (s)		Incident dementia	aSHR: 1.33; 95% CI: 1.14 to 1.56 $aSHR_{AD}$: 1.25; 95% CI: 1.05 to 1.49 $aSHR_{VaD}$: 1.64; 95% CI: 1.2 to 2.3

(*Continues*)

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Table 2 (continued)

Reference	Study	Site	Age (years)	Sample	Frailty tool	Frailty domain	Mobility	Gait protocol (walk)	Outcome	Gait influence on outcome
Rahi *et al.*, 2018[100]	LP	FRa	≥75	560	FPFC	SP	Rosow–Breslau Test		MDS	OR_{HIGH}: 0.45; 95% CI: 0.20 to 0.99
Shimada *et al.*, 2018[101]	LP	JP	>65	4570	CF	M	GS (m/s)	2 m	Incident dementia	
Tkacheva *et al.*, 2018[102]	CC	RU	>65	1220	VNP CGA	M	TUG (s)	4 m	Geriatric syndrome	
Wei *et al.*, 2018[103]	LP	CH	≥55	1162	FPFC	SP	GS (m/s)	6 m	MNA-SF	
Yoon *et al.*, 2018[104]	CP	KR	>65	104	FPFC	SP	GS (m/s) SPPB	4 m	Cognitive function	
Yoon *et al.*, 2018[105]	CC	KR	>65	48	CF	M	GS (m/s) SPPB, TUG (s), OLS, TST	4 m	Global SUVRs	
Yu *et al.*, 2018[106]	LP	CN	>65	3491	CF	M	GS (m/s) 5CST (s)	6 m	QoL Incident physical limitation Cumulative hospital stay Mortality	
Zhong *et al.*, 2018[107]	CC	CN	>50	50	FRAIL	SP	nStep, RMS, StepVar, StepReg, StepSym, GS (m/s) ABC (s), TUG (s), BBS	12 m[b]	Frailty status	
Chou *et al.*, 2019[108]	LP	JP	>60	1096	FPFC	SP	GS (m/s)	10 m[b]	CD	
Doi *et al.*, 2019[109]	LP	JP	>65	4011	CS	SC	GS (m/s), Str (m), StrVar (%)	2 m[b]	Incident dementia	$HR_{♀,GS}$: 1.71; 95% CI: 1.13 to 2.59 $HR_{♀,Str}$: 1.72; 95% CI: 1.15 to 2.57 $HR_{♀,StrVar}$: 1.61; 95% CI: 1.13 to 2.29 $HR_{♂,GS}$: 1.79; 95% CI: 1.14 to 2.81 $HR_{♂,Str}$: 2.02; 95% CI: 1.28 to 3.19 $HR_{♂,StrVar}$: 1.61; 95% CI: 1.03 to 2.50
Ehsani *et al.*, 2019[110]	CP	USA	>65	1000	FPFC	SP	GT (s) GS (m/s), GT (s), Str (m), StrVar, DBLSt (single/dual)	25 steps[b]	CS	
Gifford *et al.*, 2019[111]	CP	USA	>60	306	FPFC	SP	GS (m/s)	4.6 m	Subjective cognitive decline	$OR_{MoCA,♂}$: 4.07; 95% CI: 1.2 to 14.1 $OR_{ECog,♀}$: 0.06; 95% CI: 0.01 to 0.38
Giusti Rossi *et al.*, 2019[112]	CC	BR	>65	72	FPFC	SP	GS (m/s) TUG (s) (single/dual)	4.6 m	TUG	
Kim and Won, 2019[113]	CP	KR	>70	1887	AWGS	SP	GS (m/s) TUG (s), SPPB	4 m[b]	CI	$OR_{♀}$: 1.88; 95% CI: 1.05 to 3.36 $OR_{♂}$: 2.58; 95% CI: 1.34 to 4.99

(*Continues*)

Table 2 (continued)

Reference	Study	Site	Age (years)	Sample	Frailty tool	Frailty domain	Mobility	Gait protocol (walk)	Outcome	Gait influence on outcome
Sathyan *et al.*, 2019[114]	LP	USA	>65	641	FI-CGA (41 items)	M	GS (m/s)	8.5 m[b]	Incident MCR	HR: 1.06; 95% CI: 1.03 to 1.10
Umegaki *et al.*, 2019[115]	CP	JP		447	FPFC	SP	GS (m/s)	5 m	CS	OR_{DSS}: 0.71; 95% CI: 0.54 to 0.94
Zhou *et al.*, 2019[116]	CC	USA	>60	61	FPFC	SP	GS (m/s) iTMT (m/s, s, W, %)	4.6 m[b] 20 m	Frailty status	OR: 0.082; 95% CI: 0.007 to 0.947
Maggio *et al.*, 2020[117]	CC	IT	>75	122	9-item Sunfrail Checklist	M	GS (m/s)	4 m	Frailty status	
Özsürekci *et al.*, 2020[118]	CC	TK	>70	118	CFS-FI (9 items) FPFC	M SP	GS (m/s)	4 m	Frailty status	
Shim *et al.*, 2020[119]	CP	KR	>70	2881	MCR	M	GS (m/s) TUG (s), SPPB	4 m	CS	

♀, female; ♂, male; 5CST, five-chair stand test; 6MWT, 6 min walking test; ABC, Activity-specific Balance Confidence scale; AD, Alzheimer's disease; ADL, activities of daily living; ADU, adjusted difference per unit; AltSTEP, alternate step; AMT4, four-item version of the Abbreviated Metal Test; ApEn, approximate entropy; A-PH, anthropometry and physical performance; aSHR, adjusted subdistribution hazard ratio; AWGS, Asia Working Group for Sarcopenia criteria; BAL, balance; BBS, Berg Balance Scale; BE, behavioural aspects; BEl, Belgium; BR, Brazil; CA, Canada; CAD, Cadence; CC, cross-sectional clinical-based study; CD, cognitive decline; CDT, Clock Drawing Test; CES-D, Center for Epidemiologic Studies Depression Scale; CF, cognitive frailty; CFM, composite frailty measure; CFS-FI, Clinical Frailty Scale—Frailty Index; CGA, comprehensive geriatric assessment; CH, Switzerland; CI, cognitive impairment; CI, confidence interval; CN, China; COP, centre of pressure; CP, cross-sectional population-based study; CS, cognitive status; CST, chair stand test; CWS, walking speed at a comfortable pace; DBLSt, double support; DK, Denmark; DQI-I, Dietary Quality Index-International; DSS, digit symbol substitution; DTC, Dual Task Condition; ECog, Everyday Cognition Scale; ES, Spain; EU, European Union; FFQ, food frequency questionnaire; FI, frailty index; FI-CGA, frailty index based on comprehensive geriatric assessment; FICSIT-4, Frailty and Injuries: Cooperative Studies of Intervention Techniques-4; FPFC, Fried physical frailty criteria; FR, functional reach; FRa, France; FRAIL, Fatigue, Resistance, Ambulation, Illnesses, and Loss of Weight questionnaire; FRT, functional reach test; GFST, Gerontopole Frailty Screening Tool; GReg, gait regularity; GS, gait speed; GSym, gait symmetry; GT, gait time; HaR, harmonic ratio; HGS, hand grip strength; HR, hazard ratio; HRQoL, health-related quality of life; HS, health status; ID, Indonesia; IE, Ireland; IGF-1, insulin-like growth factor-1; IRR, incidence rate ratio; ISAR, Identification of Seniors at Risk; IST, Isaacs set test; IT, Italy; iTMT, instrumented Trail-Making Task; JP, Japan; KR, South Korea; LC, longitudinal clinical-based study; LP, longitudinal population-based study; LTCI, long-term care insurance; LWK, linear weighted kappa; M, multi-domain; MCI, mild cognitive impairment; MCR, motoric cognitive risk syndrome; MD, muscular dysfunction; MDS, Mediterranean Diet Score; MEDAS, Mediterranean Diet Adherence Screener; MFI, multidimensional frailty index; MMSE, Mini-Mental State Examination; MNA-SF, Mini Nutritional Assessment Short Form; MoCa, Montreal Cognitive Assessment; MPPT, Modified Physical Performance Test; MX, Mexico; MY, Malaysia; nGS, narrow walking speed; NH, nursing home; NL, Holland; NMC, neuromuscular composite score; NSI, Nutritional Screening Initiative Determine Checklist; nStep, number of steps; OLS, one-leg standing test; OR, odds ratio; PF, physical function; PFF, physical fitness function; POMA, Performance-Oriented Mobility Assessment; PPV, positive predictive value; PT, Portugal; QoL, quality of life; RMS, root mean square; RU, Russia; SART, Sustained Attention to Response Task; SC, single cognitive; SC, single-domain cognitive; SE, socio-economic aspects; SG, slow gait; SI, sensory impairment; SP, single-domain physical; SPPB, Short Physical Performance Battery; SS, single-domain social; StepReg, step regularity; StepSym, step symmetry; StepVar, step variability; StL, step length; Str, stride length; StrVar, stride variability; StW, step width; StWvar, step width variability; SUVR, standardized uptake value ratio; SW, Sweden; Sw, swing phase; Sway, postural oscillation; SwVar, swing variability; TaGA, targeted geriatric assessment; THD, total harmonic distortion; TR, Turkey; TST, tandem standing test; TUG, Time Up and Go test; TW, Taiwan; TWT, tandem walking test; VaD, vascular dementia; VF, verbal fluency; VNP, Vozrast ne pomekha.

[a]US states: Texas, New Mexico, Colorado, Arizona, and California.

[b]Technological devices have been used for the assessment.

[c]CN, MX, Peru, Cuba, Dominican Republic, Venezuela, and India.

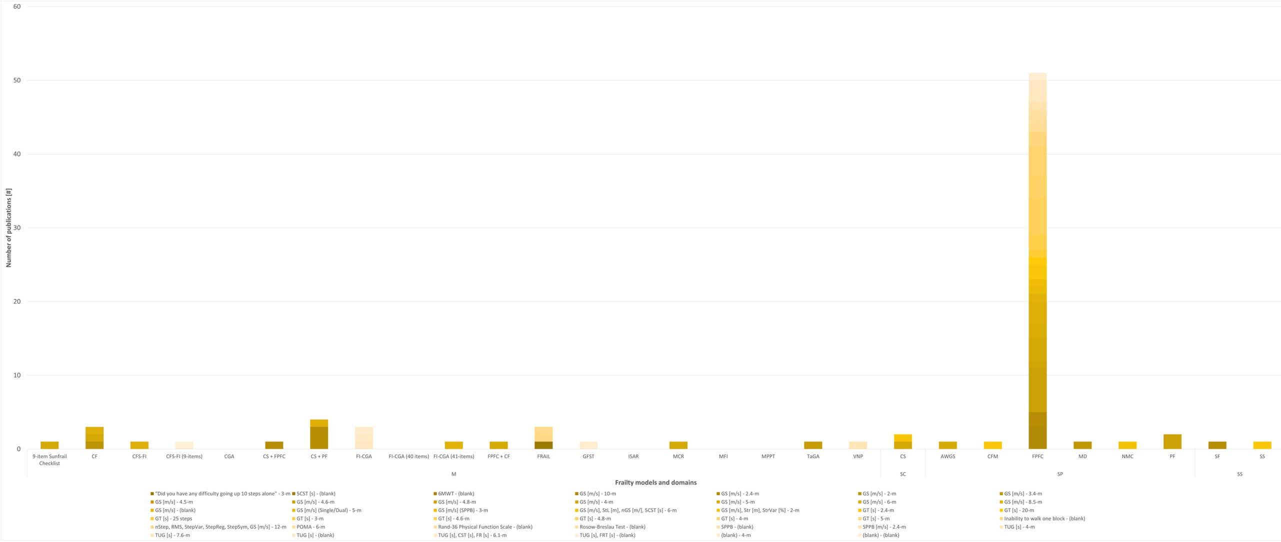

Figure 3 Distribution of included studies in relation to frailty models (and related domains) in relation to the selected gait parameters and protocols.

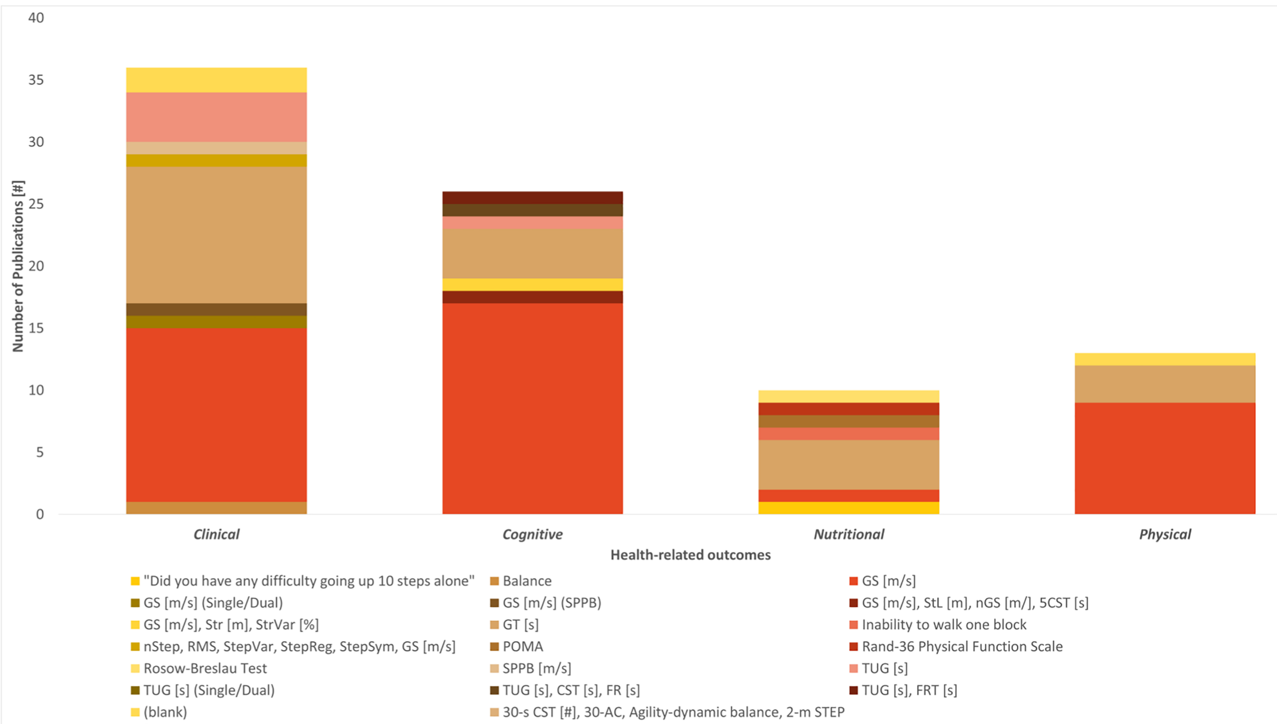

Figure 4 Distribution of included studies in relation to the health-related outcomes investigated and the gait parameters adopted.

Finally, Maggio and colleagues[117] and Özsürekci and colleagues[118] investigated the construct validity of novel frailty indices (respectively, the nine-item Sunfrail Checklist and the 9-Point CFS) through the correspondence between some checklist items with different domains, including gait speed.

The role of gait in the different categorized health-related outcomes

Clinical domain

In particular, the present findings suggest that gait speed was the strongest predictor of chronic[36] and incident disability,[66] especially in co-occurrence of MCI[67,69,70] and long-term hospital stay.[36] Four studies showed that there was a main effect of gait impairment for predicting mortality and dependence in different settings.[71,88] Brown and colleagues[55] explored these issues in the older depressed group, while Jotheeswaran and colleagues[68] in a large population-based cohort study on older people in Latin America, India, and China. Tabue-Teguo and colleagues[71] have shown that measures of gait and psychomotor speed contributed to define subjects with an increased risk of dying. Hernández-Luis and Martín-Ponce[88] showed how mortality at 100 days and long-term survival were closely related to physical function capacity in older hospitalized patients.

Finally, three studies investigated the role of gait speed in contributing to quality of life, measured in different aspects.[45,54,78] Chang and colleagues[45] reported that slowness was the major contributor to a worse score of seven of eight subscales of Short Form (36) Health Survey. Alexandre and colleagues[54] observed that in polypharmacy, joint disease and chronic pain were similarly associated with slowness. Ayers and colleagues[78] carried on the first study showing that apathy symptoms may predict incident frailty and motoric decline among non-demented, community-dwelling older adults as well being an independent risk factor.

Cognitive domain

Boyle and colleagues[39] reported, in a study that used 12 years of annual follow-up data, that physical frailty was associated with a high risk of MCI, such that each 1 unit (grip strength, timed walk, body composition, and fatigue) increase in physical frailty was associated with a 63% increase in the risk of MCI. Auyeung and colleagues[41] showed that physical frailty, as indicated by low body weight, weaker grip strength, slower performance in the chair stand test, and shorter step length in men and weaker grip strength in women, was associated with a decline in Mini-Mental State Examination (MMSE) score over a 4 year period. Montero-Odasso and colleagues[75] showed that cognitive frailty may embody two different manifestations, slow gait speed and low cognition, of a common underlying mechanism. Participants having slow gait and cognitive impairment had significantly higher incidence of dementia, 12% with an incidence rate of 130 per 1000 person-years. Veronese and colleagues[76] found that slow gait speed predicted the onset of cognitive decline at 4.4 year follow-up. Hooghiemstra and colleagues[89] found associations between slower gait speed and worse baseline performance on measures of memory, attention, information processing speed, and verbal fluency. However, cox proportional hazards models showed no associations between baseline gait speed and grip strength and clinical progression to MCI or dementia.

Nyunt and colleagues[91] reported that almost two-thirds of community-dwelling older adults with MCI manifested physical frailty or pre-frailty, including low lean muscle mass, low muscle strength, slow gait speed, exhaustion, and low physical activity, as well as balance and gait impairment, which posed elevated risk of falls, in greater proportions compared with their cognitively normal counterparts. Doi and colleagues[96] showed that co-occurrence of MCI and slow gait speed had a high risk of dementia compared with that of each condition alone. Garcia-Cifuentes and colleagues[85] reported that Colombian older adults who had low handgrip strength and gait speed had an increased risk to suffer of cognitive impairment, regardless of age, sex, education, or body mass index (OR: 2.76; 95% CI: 1.83–4.15). Hartley and colleagues[87] reported a relationship between the pre-admission levels of frailty, as assessed by the CFS, which is based on clinical judgement, and objectively measured usual walking speed, assessed on the day of discharge from hospital. They observed a strong association between higher admission CFS and lower discharge usual walking speed, regardless of variation in age, sex, presence of cognitive impairment, or illness acuity. Hsueh and colleagues[98] demonstrated a positive relationship between frailty and Alzheimer's Disease 8 scores, a brief questionnaire used to differentiate normal aging from dementia, among older individuals showing that the OR of frailty for individuals with Alzheimer's Disease 8 scores ≥ 2 was 5.3.

Yassuda and colleagues[49] firstly added new information to the international literature on frailty and cognition as it included other cognitive measures (delayed memory recall, verbal fluency, and Clock Drawing Test), in addition to the MMSE, showing that frail older adults more frequently presented with cognitive impairment. They also found that gait speed was associated with executive functions (verbal fluency and Clock Drawing Test). McGough and colleagues[52] reported similar results in a baseline cross-sectional analysis of data coming from a randomized controlled trial of psychosocial and exercise interventions for sedentary older adults with amnestic MCI. They found that faster usual gait speed was associated with lower severity of cognitive impairment, as measured with the Alzheimer's Disease Assessment Scale-Cognitive Subscale. In addition, faster usual gait speed was associated with better performance in cognitive dimensions of attention, executive function, and immediate recall. Shimada and colleagues[53] reported the prevalence of combined physical and cognitive decline in a sample of 5104 older community dwellers in Japan (2.7%). In a subsequent prospective study, the same authors found that dementia risk was significantly associated with cognitive impairment and cognitive frailty; in particular, the dementia incidence risk in the cognitive impairment and cognitive frailty groups was 2.1 and 3.4 times higher than in the healthy group, respectively.[101] O'Halloran and colleagues[57] investigated whether sustained attention performance and variability were associated with pre-frailty and frailty in the Irish Longitudinal Study on Aging. They found that the fast variability measure was only the mean reaction time and fast variability measures were significantly associated with pre-frailty and frailty. In addition, among the younger 50–64 age group, a 1 SD increase in mean reaction time correlated with a 39% increased risk of being frail on the low gait speed component, while among the older 65+ age group, a 1 SD increase in the fast variability measure was correlated with a 31% increased risk of being frail on the low gait speed. Chou and colleagues[108] showed that the slowest gait speed group showed a significantly greater decline in Digit Symbol Substitution Test scores, a test evaluating processing speed, over 10 years than the highest group, but not in the MMSE scores. Kim and Won[113] recently reported that cognitive impairment domains, such as processing speed and executive function, were associated with sarcopenia-related slow gait speed. Umegaki and colleagues[115] demonstrated that pre-frailty was associated with lower memory and processing speed performance, but not with other cognitive domains. Among the components of the physical phenotype of frailty, slow gait speed and loss of physical activity were significantly associated with slow processing speed as assessed by the Digit Symbol Substitution Test.

Fougère and colleagues[83] analysed the relationship between cognition and the components of the physical phenotype of frailty. Their results supported the idea that physical frailty, and more specifically slow gait speed, was associated with cognitive impairment. Yoon and colleagues[104] reported that slowness presented significant correlations with processing speed, working memory, and memory in older rural residents. Yu and colleagues[106] found that cognitive frailty may be defined as the occurrence of both cognitive impairment and pre-frailty, not necessarily progressing to dementia. In fact, compared with participants who were robust and cognitively intact at baseline, those who were pre-frail and with overall cognitive impairment had lower grip strength, lower gait speed, poorer lower limb strength, and poorer performance in memory delayed recall at Year 4. These cognitive frail subjects had also an increased risk of poor quality of life and incident physical limitation at Year 4, increased cumulative hospital stay at Year 7, and mortality over an average of 12 years after adjustment for covariates. Sathyan and colleagues[114] reported that higher levels of frailty, diagnosed using a 41-point cumulative deficit frailty index where slow gait was not included, increased risk for developing motoric cognitive risk syndrome (MCR). Shim and colleagues demonstrated that individuals with MCR had an increased risk of poor cognitive profile related to brain frontal and prefrontal function, because they observed that MCR was associated with deficits in global cognition, processing speed, and executive function, but not delayed free recall memory.[119] Increasing gait speed related to lower Everyday Cognition Scale total score, quantifying subjective cognitive decline, and lower memory scores has been observed by Gifford and colleagues[111] who also suggested a possible sex difference in the clinical manifestation of frailty, with primary associations noted in women. De Cock and colleagues[80,95] suggested that multifactorial gait analysis could be more informative than using gait analysis with only one test or one variable. They confirmed that gait speed, mean number of steps per metre (similar to step or stride length) and swing time variability (equal to step time variability), was associated with the severity of cognitive impairment at usual pace. These findings were confirmed also by Doi and colleagues[109] who suggested that gait speed, stride length, and stride variability were significantly related to incident dementia among the full sample. Only two studies suggested that alternative methods, like Time Up and Go (TUG) test[99] or Upper-Extremity Function,[110] may provide a more sensitive and specific model for predicting cognitive status in comparison with gait because walking is a routine daily activity, minimum skill learning is involved in its performance.

Finally, two studies investigated the role of Dual Task Condition during gait in characterizing frailty subjects and frail with cognitive impairments[59,74]: they concluded that gait performance was significantly different in regularity and symmetry for both the frail and frail with cognitive impairment groups compared with the control group, but no differences were observed between the frail and frail + MCI groups. These results indicated that the performances related to the dual-task costs were likely independent of the MCI level. A possible explanation for the lack of differences in the functional tests between the frail individuals with and without MCI was the sample size and the fact that the categorization of gait impairments has not yet been studied using the dual-task paradigm.

Physical domain

Rothman and colleagues[36] carried on a longitudinal study of 754 initially nondisabled, community-living persons aged 70 and older for 96 months. They found that slow gait speed was the only significant predictor of injurious falls (hazard ratio: 2.19; 95% CI: 1.33–3.60). Shimada and colleagues[38] showed that clinical tests of neuromuscular functioning may be able to predict risk of falling in frail older people. In fact, in the validation study, univariate analyses identified several tests as being able to discriminate between fallers and non-fallers (one-leg standing test, tandem walking test, 6 m walking speed at a comfortable pace, 6 m walking speed at maximum pace, and TUG tests). In contrast, only the tandem walking test was identified as a clinically relevant independent predictor of falls by multiple logistic regression analysis. When performance was dichotomized, only the 6 m walking speed at a comfortable pace, one-leg standing, and 6 m walking speed at maximum pace tests remained statistically significant predictors of falls. Langlois and colleagues[46] found that physical capacity measures (i.e. functional capacities, physical endurance, gait speed, and mobility) were significantly lower in frail participants.

Doi and colleagues[67] supported the idea that slow gait and MCI were related and concurrently associated with falling (OR: 1.99; 95% CI: 1.08–3.65), collected as fall history in a face-to-face interview. Similar findings have been previously observed by Casas-Herrero and colleagues,[51] where the authors reported an association between the decrease in gait speed with arithmetic tasks (Dual Task Condition) during the TUG test with the risk of falls (assessed using questionnaires) in both the frail and frail + MCI groups, even though no differences were observed between the two groups in the physical outcomes. Finally, Malini and colleagues[73] assessed fear of falling by Falls Efficacy Scale International in a cross-sectional study on 742 participants from the Research Network Frailty in Brazilian Older People, specifically the Rio de Janeiro section. They found that diminished gait speed was associated with fear of falling (OR: 1.64; 95% CI: 1.04–2.58). Martínez-Ramírez and colleagues[74] revealed no significant differences in gait kinematic performance between the frail + MCI and frail groups for either the habitual gait test or the dual-task gait tests. Nevertheless, the kinematic parameters demonstrated significantly better performance for the control group than the frail and frail + MCI groups. Furtado and colleagues[84] reported that significant correlations were found between FS and endurance, agility–dynamic balance, and upper and lower limb muscle strength tests.

In a large cross-sectional study, Yamada and colleagues[58] showed that visual and hearing impairments were associated with higher rates of balance problems, defined as exhibiting difficulty in standing, difficulty turning around, dizziness, or unsteady gait. Subsequently, in the Health, Aging and Body Composition study, Kamil and colleagues[121] demonstrated that older adults with moderate-or-greater hearing impairments had a 63% increased risk of being frail, defined as a gait speed of $<$0.60 m/s and/or inability to rise from a chair without using arms.

Yoon and colleagues[105] explored the associations between accumulation of amyloid-β in the brain as a brain imaging biomarker and phenotypes of physical frailty (weight loss, weakness, exhaustion, slowness, and low physical activity) in older adults with MCI and cognitive frailty from the Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease. They found that mean cortical region of interest and regional standardized uptake value ratios were associated with gait speed, TUG, and Short Physical Performance Battery.

Three studies investigated the relationship among gait speed and insulin-like growth factor-1 (IGF-1).[65,72,97] They found that low serum IGF-1 was associated with reduced cognitive function and gait speed, particularly with a combination of MCI and slow gait,[65,97] predicted incident disability among community-dwelling older adults,[72] thus confirming the hypothesis that decreased IGF-1 is considered to be caused by cumulative molecular and cellular damage and leads to frailty in older population.[97] Dokuzlar and colleagues[81] reported no significant difference in sub-parameters of the Fatigue, Resistance, Ambulation, Illnesses, and Loss of Weight questionnaire (Morley and colleagues[122]) and the physical frailty phenotype operationalized with Fried criteria[34] (specifically ambulation and slowness) between patient groups divided based on vitamin B12 level above or below 400 pg/mL or state of frailty.

Finally, Camicioli and colleagues[61] examined if handwriting parameters were associated with gait performance, weakness, poor endurance/exhaustion, and cognitive impairment. They reported that gait was not significantly associated with overall writing velocity although lower overall writing velocity was found in subjects characterized by slow gait velocity. Hanton and colleagues[86] identified statistically significant differences between functionally intact and frail participants in mobile phone-derived measures of per cent activity, active vs. inactive status, average step counts, and gait speed.

Nutritional domain

Several interrelated factors may contribute to the aetiopathogenesis of frailty syndrome. Significant body of evidence is available regarding the relationship among insufficient protein and caloric intake with sarcopenia and frailty.[123] In the InCHIANTI study, Bartali and colleagues[35] found that daily energy intake $\leq$ 21 kcal/kg body weight was significantly associated with frailty (OR: 1.24; 95% CI: 1.02–1.5). This study also analysed the association between frailty and nutrients, and after adjusting for energy intake, low intakes of protein (OR: 1.98; 95% CI: 1.18–3.31), vitamin D (OR: 2.35; 95% CI: 1.48–3.73), vitamin E (OR: 2.06; 95% CI: 1.28–3.33), vitamin C (OR: 2.15; 95% CI: 1.34–3.45), and folate (OR: 1.84; 95% CI: 1.14–2.98) were significantly and independently related to frailty. However, they found no association between gait-related criteria and frailty phenotype. In the Women's Health and Aging Studies, Beasley and colleagues[42] showed that a 20% increase in uncalibrated protein intake (% kcal) was associated with a 12% (95% CI: 8–16%) lower risk of frailty and that a 20% increase in calibrated protein intake was associated with a 32% (95% CI: 23–50%) lower risk of frailty.

Two studies showed an association between Mediterranean diet [based on a Mediterranean Diet Score (maximum 9 points) evaluated by an interview-based food frequency questionnaire] and frailty.[48,50] In the InCHIANTI study, 690 patients aged $\geq$65 years were included and followed up for 6 years. Results showed that higher adherence (score $\geq$ 6) to a Mediterranean-style diet was associated with lower odds of developing frailty (OR: 0.30; 95% CI: 0.14–0.66) compared with those with lower adherence (score $\leq$ 3) and that higher adherence to a Mediterranean-style diet at baseline was also associated with a lower risk of low physical activity (OR: 0.62; 95% CI: 0.40–0.96) and slow walking speed (OR: 0.48; 95% CI: 0.27–0.86), but not with feelings of exhaustion and poor muscle strength.[48] In another study, Bollwein and colleagues[50] showed that the risk of being frail was significantly reduced in the highest quartile of the Mediterranean Diet Score (OR: 0.26; 95% CI: 0.07–0.98). In line with these results, León-Muñoz and colleagues[56] observed that being in the highest tertile of Mediterranean Diet Adherence Screener score was associated with a reduced risk of slow walking (OR: 0.53, 95% CI: 0.35–0.79). Furthermore, Rahi and colleagues[100] found that Mediterranean diet adherence was associated with a significantly reduced risk of incident slowness (OR: 0.45, 95% CI: 0.20–0.99). Chan and colleagues,[62] in contrast, reported no association between other dietary patterns and incident frailty. Their study showed that a better diet quality as characterized by higher Dietary Quality Index-International was associated with lower odds of developing frailty.

In a large cross-sectional study, Arjuna and colleagues[77] found that range of gait speeds observed in their study for the rural and urban participants (i.e. 0.34 to 0.72 m/s) was substantially slower than for predominantly Caucasian and Afro-American older community-living adults (0.70 to 1.42 m/s) and comparable with institutionalized Western people aged 90 years or more (0.49 ± 0.21 m/s for 90 years and 0.43 ± 0.19 m/s for 95+ years), highlighting the necessity for different cut-off values for specific ethnicities. In addition, they reported a positive correlation among biomarkers of nutritional status, such as energy and protein intake, and gait speed showing a decrease in gait speed as nutritional status changed from malnourished to at risk of malnutrition to well nourished.

Finally, Wei and colleagues[93,103] found that changes in nutritional states were associated with frailty state transitions. They reported that Mini Nutritional Assessment at risk/malnutrition was highly significantly associated with pre-frailty (OR: 2.11; 95% CI: 1.80–2.46; OR: 6.71; 95% CI: 3.43–13.1) and frailty (OR: 2.72; 95% CI: 1.84–4.02; OR: 17.4; 95% CI: 6.68–45.3). Also, in one of the studies (Wei *et al.*[103]), being at risk of malnutrition/malnourished at baseline was associated with increased odds of prevalent pre-frailty (OR: 2.76; 95% CI: 1.86–4.10) and frailty (OR: 4.10; 95% CI: 1.41–11.9) as baseline robust individuals who were persistently at risk of malnutrition/malnourished showed an increased odds of conversion to being pre-frail/frail at follow-up (OR: 3.45; 95% CI: 1.00–11.9). However, no specific contribution of slowness has been investigated in relation to the nutritional status.

Discussion

In the present systematic review, retrieving and evaluating original studies that assessed how gait is measured in the frail population and how the gait parameter adopted may influence the estimated frailty phenotype and health-related outcomes, gait appeared to be an indicator of health and function also in frail older adults. No previous attempts have been made in trying to clarify the complexity and the multidimensionality of gait in different settings and with different frailty models or tools. We were then able to highlight the great heterogeneity in measurement protocols in both clinical-based and population-based settings that could represent an important issue causing variability in the different outcome measures. For different frailty phenotypes, some studies reported that not only gait speed but also other gait parameters may help in categorizing either frail subjects and the combination of frailty and MCI (cognitive frailty phenotype) and that all physical function tests significantly varied between social frailty groups (social frailty phenotype). Therefore, combining various gait parameters may enhance frailty prediction and classification of different frailty phenotypes. Gait parameters appeared to predict adverse health-related outcomes in clinical, cognitive, and physical domains and, to a lesser extent, in nutritional domain, as shown in *Figure* 2 and extensively discussed in the Results section.

The transition from a robust status to one of age-related disability is usually preceded by a physiological state termed frailty.[4,124] Although frailty can be characterized using classical clinical phenotypes and laboratory-based biomarkers, a consensual definition of frailty has been proposed, but an operational assessment remains to be agreed upon.[5] In fact, this clinical construct may include sensorial, physical, social, cognitive, psychological/depressive, and nutritional phenotypes.[125] Therefore, it is not surprising that over 40 operational definitions of frailty have been proposed but, to date, a formal consensus is still lacking. The most prominent approach used to assess frailty is using the physical frailty phenotype.[34] Following this model, frailty is diagnosed based on the presence of at least three of the five physical attributes and capabilities of an individual. These include weight loss (unintentional weight loss of 4.5 kg or more in the last year), exhaustion (mostly self-reported), physical inactivity, slow walking speed, and weakness (low grip strength). Among these criteria, gait speed has been reported as one of the strongest to predict adverse outcomes, such as mobility disability, falls, or hospitalization. Despite this fact, gait analysis has not been used in routine assessment of frailty status. Little is known about the association between gait parameters other than gait speed and categorical frailty status. The present findings confirmed those coming from another systematic review suggesting that the combination of various spatio-temporal parameters of gait may enhance the sensitivity and specificity of frailty risk prediction and classification.[30] Adachi and colleagues[126] showed how maximum step length also showed good predictive accuracy for usual walking speed < 0.8 m/s. Recently, Grande and colleagues,[127] in another review article, summarized the evidence concerning the association of slow gait speed with cognitive decline and dementia and discussed the possible shared pathways leading to cognitive and motor impairments, under the

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unifying hypothesis that body and mind are intimately connected. They concluded that the measurement of gait speed may improve the detection of prodromal dementia and cognitive impairment in individuals with and without initial cognitive deficits.

Limitations of the present systematic review included the inability to combine aggregate-level data reported in each primary study to perform a meta-analysis in order to strengthen our work. Thus, we were not able to state that we recognized the specific contribution of one or more gait parameters in the definition of frailty neither in the assessment of different outcomes. Thus, advances in technology during the last decade have provided investigators and clinicians low-cost tools for measuring not only speed but also other gait variables with high validity and practicality in research, clinical, and home settings.[128] However, a precondition for the use of this technology for routine clinical assessment is a proper understanding of the relationship between gait parameters and frailty.[129,130] Acquiring more information about gait in older adults defined as frail has been repeatedly requested[131,132] and would enhance our understanding of ambulation patterns in this vulnerable population. Moreover, this information can serve as a reference for follow-up studies.

Heterogeneity

Although most of the included studies referred to the physical frailty phenotype[34] as a mono-domain frailty tool, there were variations in the protocol to measure gait speed (*Figure* 3). Distance for the timed walk ranged from 4 to 20 m, and one study[51] measured gait speed over two distances (4.8 and 5 m). In addition, two studies reported gait measurements as categorical values,[58,95] and one study considered the number of steps walked as measure of walking abilities.[110] Another variation in the protocol was whether timing initiated from a static or moving start. Where technology-based assessment was used to measure gait parameters, a moving start was assumed. All the studies measured gait speed using a self-selected or usual pace. Other terms in the literature to denote gait speed at usual pace included comfortable, habitual, normal, or preferred. Six studies recorded gait speed also during dual task.[36,51,59,110,112] Overall, the 4 m walk is the most used version for studies in older people.

Influence of gait in different frailty models

There is a consensus on the definition of physical frailty, which is well known.[34] Almost all of the studies identified slowness as one of the most prevalent criterions in the definition of frailty status and observed that walking speed in the frail population was significantly lower than healthy controls.[40,44,63,75] Only two studies investigated the role of other components as balance in the definition of frailty[37,43] with contrasting results.

Numerous studies examined other models of frailty, focusing on cognitive and social components. With respect to the cognitive aspect of frailty, an International Consensus Group for ‘cognitive frailty’ was organized by the International Academy on Nutrition and Aging and the International Association of Gerontology and Geriatrics in 2013.[133] They provided the first definition of ‘cognitive frailty’ in older adults. Five studies recalled this operational definition,[75,101,104,105] while three other studies considered either additional measurements of cognitive status[82,106] and the recently described MRC,[28] defined as the presence of slow gait and cognitive complaints.[83] Results from these studies were in agreement with a ‘motor signature’ of cognitive decline that shows that slow gait is associated with cognitive status.

Several studies have shown that older individuals with social frailty had the highest risks of instrumental activities of daily living limitations; thus, an operational definition of this frailty phenotype using simple questions was reported to assess social engagement for older people.[134] Social frailty not only takes into account the role played by the socio-economic context in determining the vulnerability status in older age but also can be defined as a continuum of being at risk of losing, or having lost, social and general resources, activities, or abilities that are important for fulfilling one or more basic psychosocial needs during the life span.[14] Only Tsutsumimoto and colleagues[92] carried on a cross-sectional population-based study in Japan to investigate the association between social frailty and cognitive and physical function among older adults. They found that all physical function tests, characterized by slow walking speed or/and lower grip strength, significantly varied between social frailty groups.

Relationship among gait and categorized study outcomes

Over the last century, life expectancy has steadily improved worldwide, and the number and proportion of older people have markedly increased.[135] This trend is expected to continue in the next few decades, and there will be an unprecedentedly large number of older people.[135] Older adults are the main users of health care services and account for most of the health care costs. Recently, Kojima[136] found a dose–response increase in health care costs associated with frailty among community-dwelling older adults.

The present review showed that the majority of the study investigated the relationship between gait and clinical-related outcomes (36 out of 85) and almost half of the study made use of gait speed or time as parameter for gait measurement (*Figure* 4). However, the great heterogeneity in the adopted protocol did not allow us to carry out a meta-analysis of the included studies. We then summarized the major findings according to the health-related outcomes in order to clarify the contribution of gait parameters in each domain. Almost the 40% of the studies reported health-related outcomes in the clinical domain, and research findings confirmed that in both the physical and multidimensional frailty phenotypes, gait appeared to predict adverse health-related outcomes as disability, long-term hospital stays, and mortality, thus affecting quality of life.

Growing evidence has indicated that there is a connection between frailty and cognitive impairment. For the cognitive domain, in the present review, almost half of all of the included studies have reported a longitudinal association between slowness, measured as gait speed or time, and rate of MCI in older community-dwelling individuals, even though the criteria for determining frailty and MCI vary slightly between studies, as recently reported by Hoogendijk and colleagues.[137] Several studies have shown that multi-domain cognitive tests, such as those examining general cognitive function, memory, and executive function, were useful for assessing dementia risk in older individuals. Results suggested that frailty may coincide with MCI in older adults who exhibit vulnerability factors for both conditions. Therefore, the concepts of cognitive frailty[133] and MCR[28] may represent a prodromal stage for neurodegenerative diseases.

In the stage of more advanced cognitive impairment, slow gait speed did not seem to predict transitioning to death anymore. A previous scoping review by Kikkert and colleagues[138] also recommended gait analysis, including dynamic gait parameters, in clinical evaluations of patients with suspected cognitive decline. In the present review, only five studies reported that no single gait variable, but rather other gait variables or a combination of them could be used or integrated in order to classify dementia. There was only an exception with two studies reporting that the magnitude of the impairment in gait pattern was independent of frailty and cognitive impairment status,[59] probably due to the low sample size and the category (institutionalized adults). Therefore, screening for gait dynamics may be useful for identifying older adults at risk of adverse health-related outcomes such as cognitive decline.

Fall is a leading cause of mortality in older people. Incidence of fall is high among older people; one-third of older people aged 65 and older fall every year, and the incidence of falling increases up to 50% among those 80 years and older.[139] For the physical domain, in the present review, low gait speed has been reported as associated with injurious falls in three longitudinal studies, although falling risk has been assessed in different ways. Besides physical adverse outcomes as falls, associations were also found between sensorial impairments and gait speed. Identification of laboratory-based biomarkers related to frailty will contribute to a better understanding of the mechanism of advanced aging. Among such measurable biomarkers, IGF-1, an important mediator of growth hormones with protective effects on neurobiological processes and in the promotion of skeletal muscle, appeared to be associated with reduced cognitive function and gait speed, predicting incident disability among community-dwelling older adults. Preliminary investigations observed relationship between brain imaging biomarker and phenotypes of physical frailty, indicating an existing association between global standardized uptake value ratio (frontal cortex, temporal cortex, parietal cortex, precuneus/posterior cingulate cortex, hippocampus, and basal ganglia) and gait.[104]

Although several observational studies have shown an association between inadequate nutritional intake and frailty,[21] very few evidence supported the relationship among gait parameters and nutrition. Nutritional strategies focused on dietary patterns, such as a Mediterranean diet, that can be protective against frailty and the risk of slow walking speed.[48,50,56,100] A positive correlation between energy and protein intakes positively correlated with physical function (grip strength, gait speed, and Fatigue, Resistance, Ambulation, Illnesses, and Loss of Weight questionnaire) has been observed by Arjuna and colleagues[77] in rural and urban Indonesian populations. In contrast, Chan and colleagues[62] observed no association between dietary pattern and frailty, even though their findings may imply that a diet of adequate energy intake, optimal protein intake, reduced consumption of fast food, and being rich in plant-based and antioxidant containing foods, such as vegetables and fruits, is important for delaying the onset of frailty in Chinese older adults. It should be noted that different cut-off values indicating higher risk of malnutrition, frailty, and impaired physical and mental function need to be determined for specific ethnicities. Monitoring changes in nutritional status is recommended for the prevention and severity reduction of frailty among older people in the community.[123,140] As our understanding on the relationship between frailty and antioxidants continues to grow in terms of molecular mechanisms, the most convincing evidence linking antioxidant nutrition and the prevention of frailty is probably the association between adherence to Mediterranean diet (a diet rich in fruits, vegetables, and antioxidant substances) and frailty prevention that has been observed in many cross-sectional and prospective studies described earlier.[22,141]

Conclusions

The research on gait in frailty is ongoing, and a consensus on its definition is still evolving. Our systematic review highlighted a great heterogeneity in the protocols used to measure gait, even though the same frail model has been used. Such variability determined an impossibility to quantitatively compare the included studies in terms of meta-analytic results. Furthermore, little is known about the association between gait parameters other than gait speed and categorical frailty status. Because frailty is acknowledged to be a multidimensional concept and several operational definitions have been proposed, physical factors always have played an essential role. Gait speed represents one of the core elements because it is a quick, inexpensive, reliable measure of functional capacity with well-documented predictive value for major health-related outcomes.

The potential applicability of such a measure in both clinical and research settings points at the importance of expanding our knowledge about the common underlying mechanisms of cognitive and motor decline. Furthermore, combining various spatio-temporal parameters of gait may enhance the sensitivity and specificity of frailty risk prediction and classification of different frailty phenotypes. Thus, advances in technology during the last decade have provided investigators and clinicians low-cost tools, such as wearable inertial sensors and actigraphy, for measuring not only speed but also other gait variables with high validity and practicality in research, clinical, and home settings. However, whether gait should be considered a predictive or a responsive biomarker is still in debate.

Author contributions

Ilaria Bortone contributed to the conceptualization, methodology, investigation, data curation, original draft preparation, and writing—reviewing and editing; Rodolfo Sardone contributed to the conceptualization, methodology, and writing—reviewing and editing; Luisa Lampignano contributed to the investigation and data curation; Fabio Castellana and Roberta Zupo contributed to the methodology and validation; Madia Lozupone wrote, reviewed, and edited the manuscript; Biagio Moretti supervised the study; Gianluigi Giannelli supervised the study and contributed to the funding acquisition; Francesco Panza contributed to the conceptualization, validation, and writing—reviewing and editing.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Supporting Information

Table S2. Supporting Information

Table S3. Supporting Information

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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